REMARKS/ARGUMENTS

Claims 1-10 are currently pending. Claims 1, 2, 5, 7, and 9 have been amended. Support for these amendments is set forth in detail below. No new matter is added by these amendments.

Claim Objections

The Examiner has objected to claim 9 as allegedly having potentially confusing wording. Claim 9 has been amended, as suggested by the Examiner, to recite "...(a) contacting the sample with a known amount of labelled intrinsic factor and a known amount of an antibody bound to a solid phase ~~which~~, wherein the antibody specifically binds to intrinsic factor ...." Applicants believe that the skilled artisan, reading claim 9 as originally filed and in light of the specification, would understand the phrase "specifically binds to intrinsic factor" to refer to the recited antibody. Therefore, Applicants do not believe that the instant amendment narrows the scope of claim 9 in any manner.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-10 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner believes the phrase, "being released from binding in the presence, and upon the binding, of vitamin B12 to intrinsic factor," to be confusing because "all antibodies and cognate antigens are in a state of equilibrium where the antigen is continuously unbound and then rebound to the antibody."

Applicants respectfully traverse the instant rejection. Whether a claim is definite depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification. *See, North Am. Vaccine, Inc. v. American Cyanamid Co.*, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993). In the present case, the specification describes allosteric competitive anti-intrinsic factor antibodies that bind to a conformational epitope that is

distinct from the B12 binding site, such that the binding of B12 to the B12 binding site "will lead to the prompt release of previously bound antibody ..." due to a conformational change of intrinsic factor (page 6, lines 1 and 2). This "release" is further characterized as an increase in the first order dissociation rate of the antibody-intrinsic factor complex (*see, e.g.*, page 22, lines 8-13). Further, as set forth in the specification, the binding of B12 to intrinsic factor "causes the dissociation of previously bound antibody" (page 22, lines 13-17). In view of the above, the skilled artisan reading claims 1-10 in light of the specification would understand that the phrase, "being released from binding in the presence, and upon the binding, of vitamin B12 to intrinsic factor," does not mean the "release" of antibody normally associated with an antibody in equilibrium with the cognate antigen, but, rather, a release that is caused by the addition of B12, which can be determined by measuring an increase in the first order dissociation rate that is dependent on the concentration of vitamin B12. Therefore, Applicants believe claims 1-10 to be definite.

While not agreeing with the Examiner's rejection or reasons therefore, but in order to further expedite prosecution of the instant application, Applicants have amended claims 1, 2, 5, 7, and 9 to delete the phrase, "being released from binding in the presence, and upon the binding, of vitamin B12 to intrinsic factor," and to recite that the antibody exhibits "an increase in the first order dissociation rate of the antibody-intrinsic factor complex in the presence of vitamin B12, wherein the dissociation rate is dependent on the concentration of vitamin B12." Support for this amendment is found in the specification at, *e.g.*, page 22, lines 8-10. For the reasons set forth above, Applicants believe that these amendments do not change the meaning of the claims from the understanding of the skilled artisan reading the claims in light of the specification as filed. Therefore, Applicants do not believe that these amendments narrow the scope of claims 1-10.

Claim 7 further stands rejected as indefinite under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, the Examiner stating that the preamble of the claim does not correlate with the recited method steps. Claim 7 has been amended to recite in step (i), "isolating the hybridomas which secrete antibodies which bound to intrinsic factor only in the absence of

vitamin B12 and exhibit an increase in the first order dissociation rate of the antibody-intrinsic factor complex in the presence of vitamin B12, wherein the dissociation rate is dependent on the concentration of vitamin B12."

In view of the remarks and amendments set forth above, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 1-10 as indefinite under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Garrido-Pinson *et al.* (*J. Immunol.*, 97:897-912, 1966) or Samloff and Turner (*J. Immunol.*, 101:578-586, 1968) (hereinafter "Samloff"). The Examiner, believing the limitation, "being released from binding in the presence and upon the binding, of vitamin B12 to intrinsic factor," to be indefinite, does not consider this phrase to be a limitation with which to compare the claims to the prior art. Further, the Examiner states that the claims do not stipulate the conditions under which "release of binding occurs." The Examiner therefore contends that the "blocking" antibodies of Garrido-Pinson *et al.* and Samloff are the same as those recited in the claims because the blocking antibodies disclosed therein bind to intrinsic factor only in the absence of vitamin B12.

Applicants respectfully traverse the instant rejection. For the reasons set forth above, Applicants believe claims 1 and 2 to be definite. Therefore, with regard to the antibodies of the present invention, the limitation, "being released from binding in the presence and upon the binding, of vitamin B12 to intrinsic factor," must be accorded weight in comparing the claimed invention to the prior art. As set forth above in response to the Examiner's rejections under 35 U.S.C. § 112, second paragraph, the limitation, "being released from binding in the presence and upon the binding, of vitamin B12 to intrinsic factor," would be understood by the skilled artisan, reading the claims in light of the specification, to mean an allosteric competitive antibody that is released from binding due to a conformational change of intrinsic factor upon

binding of B12, which can be determined by detecting an increase in the first order dissociation rate of the antibody-intrinsic factor complex that is dependent on the concentration of vitamin B12. Neither Garrido-Pinson *et al.* nor Samloff teach or suggest such an antibody to intrinsic factor. The cited references disclose antibodies that "block" binding of B12 to intrinsic factor. In contrast, with respect to the allosteric competitive antibodies of the present invention, because these antibodies bind to a site that is distinct from the B12 binding site, the antibodies do not block binding of B12 to intrinsic factor.

Applicants further note that claims 1 and 2 have been amended as set forth above in response to the rejections under 35 U.S.C. § 112, second paragraph, to recite that the anti-intrinsic factor antibody exhibits "an increase in the first order dissociation rate of the antibody-intrinsic factor complex in the presence of vitamin B12, wherein the dissociation rate is dependent on the concentration of vitamin B12." In view of these amendments, Applicants believe the Examiner's rejections under 35 U.S.C. § 102 over Garrido-Pinson *et al.* and Samloff should be obviated.

However, the Examiner, relying on principles of inherency, has suggested that the claimed antibodies "might still read on the antibodies of Garrido-Pinson *et al.* irrespective of whether the claims are definite." The Examiner's position appears to be that the antisera disclosed by Garrido-Pinson *et al.* must contain antibodies that (a) bind to a conformational epitope of intrinsic factor in the absence of B12 and (2) because of the mechanism described in the specification, fail to bind to intrinsic factor in the presence of B12.

Applicants respectfully disagree with the Examiner's belief that the claimed antibodies are inherently anticipated. A reference inherently discloses a claim limitation only "if the prior art *necessarily* functions in accordance with, or includes," the claim limitation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 51 USPQ2d 1943, 1946 (Fed. Cir. 1999). *Accord Crown Operations International Ltd. v. Solutia Inc.*, 289 F.3d 1367, 62 USPQ2d 1917, 1923 (Fed. Cir. 2002) (holding that inherent disclosure requires that the limitation be "necessarily present"). In the present case, the antisera disclosed by Garrido-Pinson *et al.* were derived from

patients that had developed an autoimmune response to human intrinsic factor. It is well-known that the immune response to a given antigen varies even among individuals of the same species: an epitope that is immunogenic in one individual may not be immunogenic in another. This is evidenced by the fact that the antisera of Garrido-Pinson *et al.* displayed several differences in binding characteristics. (*See, e.g.*, page 911, second column, paragraph 4, stating that "[o]f the 19 sera studied, eight showed the presence of both antibodies, in two the blocking antibody only was detected, and in one only the binding antibody.") Therefore, it does not "necessarily follow" that any one of the antisera disclosed by Garrido-Pinson *et al.* contained antibodies having the characteristics recited in the claims.

While not agreeing with the Examiner's rejections or reasons therefore, but in order to further expedite prosecution of the instant application, Applicants have further amended claims 1 and 2, as suggested by the Examiner, to recite a "monoclonal" antibody. Therefore, the present rejection of claims 1 and 2, as allegedly anticipated by Garrido-Pinson *et al.*, is obviated.

In view of the above remarks and amendments, Applicants respectfully request the Examiner to reconsider and withdraw the rejections of claims 1 and 2 as anticipated under 35 U.S.C. § 102(b) by Garrido-Pinson *et al.* or Samloff.

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pourfarzaneh-I (WO 91/00519), and under 35 U.S.C. § 102(e) as allegedly anticipated by Pourfarzaneh-II (U.S. 5,310,656). The Examiner believes the competitive anti-intrinsic factor antibodies of Pourfarzaneh-I to anticipate the claims, stating that the antibodies disclosed therein would bind to intrinsic factor only in the absence of vitamin B12. Again, the Examiner gives no weight to the limitation "being released from binding in the presence and upon the binding , of vitamin B12 to intrinsic factor."

For apparently similar reasons, claim 1 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Smolka (*Gastroenterology,* 98:607-614, 1990). The Examiner believes the monoclonal antibodies of Smolka are the same as those of the claimed invention

because "Smolka teaches monoclonal antibodies to intrinsic factor that appear to inhibit the binding of cobalamin by intrinsic factor," and "[t]herefore, ... such antibodies would also be blocked from binding to intrinsic factor in the presence of vitamin B12."

Applicants respectfully traverse. As set forth above, Applicants believe claims 1-6, 9, and 10 to be definite and, therefore, that all the limitations recited therein must be accorded weight. For reasons previously noted in Applicants' response to the rejections under 35 U.S.C. § 112, second paragraph, the skilled artisan reading the claims in light of the specification would understand the limitation "being released from binding in the presence, and upon the binding, of vitamin B12 to intrinsic factor" to refer to allosteric competitive antibodies, which bind to a site on intrinsic factor that is distinct from the B12 binding site, as determined, *e.g.*, by measuring an increase in the first order dissociation rate of the antibody-intrinsic factor complex upon the addition of vitamin B12. (*See* specification at, *e.g.*, page 22, lines 1-17.) Applicants also note that claim 9 expressly recites "... said antibody being capable of binding to a site on intrinsic factor that is distinct from the site on intrinsic factor to which vitamin B12 binds ...."

In contrast, the competitive antibodies disclosed by Pourfarzaneh-I and Pourfarzaneh-II are those antibodies that bind to the B12 binding site of intrinsic factor and, therefore, block B12 binding to intrinsic factor. (*See* Pourfarzaneh-I at, *e.g.*, column 3, lines 27-32, and Pourfarzaneh-II at, *e.g.*, page 5, lines 27-33, characterizing the monoclonal antibodies described therein as those either specific to the intrinsic factor:vitamin B12 complex or specific to the vitamin B12 binding site on intrinsic factor.) Similarly, Smolka discloses anti-intrinsic factor antibodies that "inhibited ... the binding of cobalamin by intrinsic factor." As noted previously, the allosteric competitive antibodies of the present invention do not bind to the B12 binding site and do not block binding of B12 to intrinsic factor.

Therefore, for the reasons set forth above, Applicants believe claims 1-6, 9, and 10 to be novel over Pourfarzaneh-I, Pourfarzaneh-II, and Smolka.

While Applicants disagree with the Examiner's rejection and reasons therefor, Applicants further note that the present rejection is obviated in view of the amendments to claims 1, 5, and 9 as set forth above in response to the Examiner's rejections under 35 U.S.C. § 112, second paragraph. These amendments clarify that the claimed antibodies exhibit an increase in the first order dissociation rate of the antibody-intrinsic factor complex upon the addition to the B12. As set forth in the specification, such an increase in the first order dissociation rate is only possible if the antibody binds to a site that is distinct from the B12 binding site. (*See, e.g.*, page 22, lines 10-13.)

In view of the above remarks and amendments, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 102 of claims 1-6, 9, and 10 as anticipated by Pourfarzaneh-I and Pourfarzaneh-II, and of claim 1 as anticipated by Smolka.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 16 June 2004 By: Brian W. Poor

Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel. No.: 206-467-9600
Fax No.: 415-576-0300
BWP/NVS/mmm
60164617 v1